Fetal megacystis

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Fetal megacystis: a lot more than LUTO

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Running head: Practical guide for excluding congenital syndromes

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Abstract

Objective: Megacystis represents a challenge in terms of counseling and management due to its various etiology and evolution. The aim of this study is to present a comprehensive overview of the underlying etiologies and structural anomalies associated with fetal megacystis.

Methods: This was a retrospective multicenter study carried out at the Fetal Medicine Units (FMUs) of the eight Academic Hospitals in the Netherlands. For each case referred to one of these centers due to fetal megacystis, data and measurements of fetal urinary tract and associated structural anomalies were collected. All available postmortem examinations and postnatal investigations were reviewed in order to establish the final diagnosis. In the first trimester, fetal megacystis was defined as a bladder with a longitudinal diameter (LBD) ≥ 7 mm, and in the 2nd and 3rd trimester as an enlarged bladder failing to empty during an extended US examination lasting at least 40 minutes.

Results: Out of 541 megacystis, megacystis was isolated (or merely accompanied by other signs of LUTO) in 360 cases (66%); and associated with other abnormal ultrasound findings in 181 cases (34%). The most common associated anomaly was an increased nuchal translucency (NT22%), followed by SUA and cardiac defects (10%). A final diagnosis was established in 418 cases, including 222 cases with isolated LUTO (53%) and 60 infants (14%) with normal micturition or isolated urological anomalies. In the remaining 136 cases (33%), a genetic syndrome, developmental or chromosomal abnormality was diagnosed.

In total, 40 chromosomal abnormalities were diagnosed, including: Trisomy 18 (n = 24), Trisomy 21 (n = 5), Turner syndrome (n = 5), Trisomy 13 (n = 3) and deletion 22q11 (n = 3). Thirty-two cases presented with Ano-Rectal Malformations involving anus, rectum and urogenital tract. In cases with confirmed urethral and anal atresia, megacystis occurred early in pregnancy and the bladder appeared severely distended (the longitudinal diameter was equal or greater than twice the gestational age). Fetal macrosomia was detected in 6 cases and an overgrowth syndrome was detected in other 4 cases: 2 infants with Beckwith–Wiedemann and 2 infants with Sotos syndrome. Megacystis-microcolon-intestinal hypoperistalsis syndrome was diagnosed in five cases (1%) and prenatally suspected only in one case.

Conclusions: Although the main cause of megacystis is LUTO, an enlarged fetal bladder can also be present as corollary finding of miscellaneous genetic syndromes, developmental disturbances and chromosomal abnormalities. This study provides an overview of the structural anomalies and congenital

disorders associated with megacystis and proposes a flowchart for the differential diagnosis of genetic syndromes, chromosomal and developmental abnormalities, focusing on the morphological examination of the fetus.

Introduction

Fetal urine production begins at about 10 weeks' gestation, when the urinary bladder can be identified as an anechoic structure within the fetal pelvis, surrounded by the two umbilical arteries[1]. The evidence of a distended urinary bladder, also known as megacystis, is an ultrasound finding as easily identifiable as hardly manageable, due to its various etiology and uncertain evolution. In the first-trimester, fetal megacystis is defined by a longitudinal bladder diameter (LBD) greater than 7 mm and is reported in 0.06% of pregnancies[2]. Beyond the first trimester, prevalence of megacystis remains unclear and its definition is still ambiguous[3].

The main cause of fetal megacystis, diagnosed at any trimester in pregnancy, is bladder outlet obstruction, also known as Lower Urinary Tract Obstructions (LUTO)[4,5,6]. In cases with severe early megacystis, parents often choose for termination of pregnancy. In less severe cases with early megacystis (with LBD ≤12 mm) and negative work-up, a spontaneous resolution often occurs[4,6,7]. In fetuses surviving the second half of pregnancy LUTO commonly leads to hydronephrosis, renal dysplasia and severe oligohydramnios with a known poor prognosis. However, besides isolated LUTO, the differential diagnosis of fetal megacystisshould also include chromosomal abnormalities, genetic syndromes and developmental anomalies. The wide spectrum of etiologies and prognoses makes the counseling and management of this condition particularly challenging[8]. Given the low prevalence of megacystis[9,10]and the main focus on LUTO as etiology, the other causes of enlarged bladder have been thus far poorly investigated.

The main aim of this study is to present a comprehensive overview of the underlying etiologies and structural anomalies associated with fetal megacystis and to identify patterns of anomalies and US features related to specific complex anomalies and syndromes, beyond LUTO.

Methods

This study is part of a large retrospective multicenter study carried out at the Fetal Medicine Units (FMUs) of all eight Academic Hospitals in the Netherlands, acting as referral centers for fetal anomalies detected at ultrasound examination. Cases with fetal megacystis were retrieved from local databases according to when registration in the databases had started (from year 2000 to 2014 at Erasmus Medical Center, Academic Medical Center, Amsterdam and at the University Medical Center, Maastricht; between 2004 and 2015 at the University Medical Center Groningen and at the Radboud University Medical Center, Nijmegen; between 2007 and 2014 in the remaining centers). In the first trimester fetal megacystis was defined as a bladder with longitudinal diameter (LBD) ≥ 7 mm (2), and in the 2nd and 3rd trimester as an enlarged bladder failing to empty during an extended US examination lasting at least 40 minutes[11].

In the Netherlands, all cases suspected for megacystis are referred to one of the eight FMUs for confirmation of diagnosis and further investigations. Cases were referred after either a dating scan, first-trimester scan, 20-week anomaly scan or after a scan performed on other indications later in pregnancy. All cases had undergone a detailed anomaly scan, except for those pregnancies that had not reached the 18th week of gestation (n = 142, including 115 pregnancies terminated and 27 miscarriages). Parents were counseled about the prognosis and informed about the possibility of in-utero treatment. The vesico-amniotic shunt placement was only offered to chromosomally normal male fetuses with isolated signs of LUTO and with concomitant oligohydramnios.

For each case, the following prenatal data were collected: gestational age at diagnosis (GA), longitudinal bladder diameter (LBD) and associated US findings. The LBD wasobtained from a mid-sagittal view of the fetus, by measuring the distance from fetal bladder dome to bladder neck. The US findings typically associated with LUTO, such as hydronephrosis, abnormal renal cortical appearance, keyhole sign and oligohydramnios (with eventual compression deformities), were not regarded as associated US anomalies. The nuchal translucency was considered increased if greater than the 95th percentile according to the GA[12]. We considered the NT measured at referral for cases referred in the first trimester of pregnancy while, in fetuses referred later in pregnancy, we retrospectively collected the NT measurement.

All available postmortem examinations and postnatal investigations were reviewed in order to establish a final diagnosis. LUTO was defined as a bladder outlet obstruction caused by urethral valves, urethral stenosis or urethral atresia. With the term Ano-Rectal Malformation (ARM) reference is made to a group of complex congenital anomalies characterized by an abnormal development of the urorectal septum,

therefore resulting in congenital abnormalities of the distal anus, rectum and genitourinary tract[13]. Among this group, cloacal dysgenesis or cloacal malformations were characterized by the absence of anal, genital and urinary orifices[14]. VACTERL association was diagnosed if three of the following criteria were met: Vertebral defects, Anal atresia/imperforate anus, Cardiovascular anomalies, Tracheo-esophageal fistula or Esophageal atresia, Renal anomalies and Limb defects (including radial anomalies) in at least two of the three regions involved (thorax, pelvis/lower abdomen and limb)[15]. Caudal regression spectrum (CRS) was defined by the occurrence of abnormalities at the level of caudal spinal segments, ranging from minor sacrococcygeal malformations to complete absence of sacrum and lumbar spine[16]. OEIS complex was diagnosed in case of Omphalocele associated with bladder Exstrophy, Imperforate anus and Spinal defect[17]. Infants without LUTO or other severe congenital abnormalities or congenital syndromes were included in the group with normal urinary tract or isolated urological anomaly, such as vesico-ureteral reflux (VUR) or duplex collecting system. In case of isolated LUTO, the postnatal renal function was evaluated by considering the estimated glomerulaater filtration rate (eGFR): this was calculated using the Schwartz formula and by taking into account the infant's length and the creatinine *nadir* in the first year of diagnosis[18].

Results

During the study period, 541 pregnancies (25 twin and 516 singleton pregnancies) were referred to one of the eight Fetal Medicine Unit in the Netherlands owing to the finding of fetal megacystis. Out of 541 cases, 233 pregnancies (43%) were referred before the 18th week of gestation (early megacystis), and 308 cases (57%) at or after the 18th week of gestation (late megacystis; figure 1). This study has dealt with structural anomalies, genetic syndromes, and developmental or chromosomal abnormalities associated with megacystis. Other outcome measures relative to this cohort have been reported on different studies[4,5,6].

Fetal megacystis was isolated (or merely associated with other signs of LUTO) in 360 cases (66%), and associated with other abnormal US findings in 181 cases (34%). In 70 cases, more than a single associated anomaly was found and in a total of 293 associated US findings were observed (Table 1). Overall, the most common associated US anomaly was an increased NT (22%), followed by a SUA and cardiac defects (10%).

Overall 88 pregnancies (35%) were terminated, 50 (9%) resulted in intra-uterine deaths (9%), 68 (13%) in neonatal deaths,and 235 (43%) children were live-born. Of the terminated pregnancies, parents did not consent to postmortem examination in 117 (62,2%) cases. Six cases were lost to follow-up (Figure 1). A final causal diagnosis was thus possible in 418 cases (77%), including 222 cases (53%) with isolated LUTO, 60 infants (14%) with another minor isolated urological anomaly or normal urinary tract anomaly at birth and 136 (33%) 'syndromic' cases with miscellaneous chromosomal abnormalities, genetic syndromes or developmental anomalies (Table 2). This last group consisted of four categories: 1) major chromosomal abnormalities (n = 40), 2) ARM (n = 32), 3) fetuses with macrosomia or overgrowth genetic syndromes (n = 10) and 4) other cases with multiple congenital abnormalities (MCA) or other miscellaneous genetic syndromes (n = 54). Table 3 summarizes GA at referral, LBD, fetal gender, amniotic fluid (AF) volume, pregnancy outcome and findings at postnatal or postmortem investigations in the syndromic cases. In table 4, we report outcome and postnatal renal function of cases with isolated LUTO.

In total, 40 chromosomal abnormalities were diagnosed (table 2 and 3), with a predominance of trisomy 18 (24 cases, including 22 with trisomy 18, and 2 with trisomy 18 mosaicisms), followed by trisomy 21 (5 cases), Turner syndrome (5 cases: 1 with Turner syndrome and 4 with Turner mosaicisms), trisomy 13 (3 cases) and deletion 22q11 (3 cases). In the chromosomally abnormal fetuses megacystiswas diagnosed at a mean GA of 17 weeks and was associated with increased NT or other severe structural anomalies. AF

volume was normal in 30% of cases. In addition, 5 fetuses presented with miscellaneous chromosomal abnormalities of unclear clinical significance and likely unrelated to the observed phenotypes.

Thirty-two cases presented with a wide spectrum of developmental abnormalities involving anus, rectum and urogenital tract, and classified as ARM. This group included: 13 VACTERL associations, 6 cloacal malformations, 7 OEIS complex, 2 Fraser syndrome and 4 CRS. In fetuses with ARM, megacystis was detected already early in pregnancy (mean GA at referral: 16 weeks). In all cases with urethral and anal atresia, fetal bladder was severely distended with LBD equal or greater than twice the GA, while in case of moderate bladder distension, with LBD lower than GA x 2 mm, a spinal or vertebral anomaly was found either at the antenatal scan or at the postmortem examination. In this group, the AF volume was reduced in 66% of cases.

Fetal macrosomia was detected in 6 cases and an overgrowth syndrome in other 4 cases: 2 infants with Beckwith–Wiedemann (BWS) and 2 infants with Sotos syndrome.

Megacystis-microcolon-intestinal hypoperistalsis syndrome (MMIHS) was diagnosed in 5 fetuses, 4 of which had normal AF volume during pregnancy. Moreover, a similar phenotype with intestinal hypoperistalsis and detrusor hypotonia was observed in one infant with Ochoa syndrome. Other miscellaneous genetic and structural anomalies observed are reported in Table 3.

Based on the antenatal findings and final diagnosis, a flowchart was designed to guide the differential diagnosis of fetal megacystis and rule out major genetic syndromes and developmental abnormalities (Figure 2).

In our study population, 360 fetuses had isolated megacystis (megacystis without other associated US abnormality or merely with associated signs of LUTO). This subgroup of fetuses showed a better outcome as reported on Figure 3. Their GA at onset of oligo or anhydramnios was related to fetal outcome. This was 17 weeks in the pregnancies that were terminated (n = 116), 20 weeks in pregnancies that ended in a IUFD (n = 19), 24 weeks in those that resulted in a neonatal death (n = 28) and 30 weeks in children that survived (n = 197). Among the 197 alive children, LUTO was confirmed in 129 cases, while in the remaining 70 a normal micturition or an isolated urological anomaly (including vesicoureteral reflux or duplex collecting system) was diagnosed. A severely impaired renal function within the first year of life (< 30 mL/min/1.73m^2) was observed in sixteen children with confirmed LUTO and in only one child without LUTO, but with severe vesico-ureteral reflux.

Discussion

This study shows that, although the main cause of megacystis is LUTO, an enlarged fetal bladder can also be present as corollary finding of miscellaneous genetic syndromes, developmental anomalies and chromosomal abnormalities. The main problem in the work-up of megacystis remains its definition and definition of a standardized antenatal approach[3]. With this study we provide an overview of the underlying etiologies and propose a flowchart to guide the differential diagnosis of cases with isolated or associated bladder enlargement.

Megacystis was associated in 1:3 cases. After exclusion of chromosomal anomalies, the most frequently complex anomaly was an ano-rectal-malformation (ARM), diagnosed in 8% of cases. Among this group, fetuses with a cloacal malformation typically presented with a severe and early megacystis with a LBD larger than twice the GA. This anomaly is typically suspected in female fetuses with distended bladder and, behind it, a single or septate anechoic area corresponding to the vagina[19-22]. In spite of a predominance in female, we confirm, similarly to other studies[19,14], that a cloacal malformation can also occur in male fetuses.

In 81% of cases (16:32), ARM was part of multisystem anomalies, such as VACTERL association, CRS, OEIS complex and Fraser syndrome. Similarly to Bornes et al., we diagnosed VACTERL association and OIES complex in 20/418 (5%) of fetuses with megacystis. VACTERL association is rarely diagnosed prenatally as the key features, such as anorectal and esophageal atresia (absence of gastric bubble) are not easily detected prenatally[20,21]. In fact, absent or small stomach bubble is only present in less than 10% of esophageal atresia, due to the presence of a trachea-esophageal fistula in the majority of cases[22]. Similarly, absence of the perianal muscular complex in anorectal atresia is more commonly observed from 23 weeks gestation onwards[23,24] and is not part of the routine 20-week scan. In light of this study, we advise to consider this condition in the differential diagnosis of megacystis, in particular if this occurs early in pregnancy with associated spinal, renal, limbs or cardiac defects, single umbilical artery (SUA) and umbilical cord cysts (UCC).

A second striking result of this study was the association of megacystis with overgrowth syndromes (4 cases) and fetal macrosomia. Megacystis was in fact reported in 2 cases of BWS and Sotos syndrome, respectively. In this group, megacystis may be due to a multiplicity of causes: such as obstructive polyps or

posterior urethral valves in BWS[25,26,27] and urethral stenosis in Sotos syndrome[28], or simply be due to polyuria. Typical antenatal US features of overgrowth syndromes have been described in detail[29], and Vora et al. proposed an algorithm to assist in the differential diagnosis of these syndromes[30]. However, it must be remembered that overgrowth/ macrosomia is rarely detected at the 20-week scan and in the majority of cases the diagnosis only occurs after birth[30].

MMIHS was only observed in 1% of cases in our cohort. This is a rare syndrome with poor prognosis characterized by a distended non-obstructed bladder and intestinal hypoperistalsis[31]. MMIHS is considered the most severe form of a spectrum of chronic intestinal pseudo-obstructive disorders, such as to the more common Hirschsprung's disease[32].The genetic basis of MMIHS has been ascribed to a number of different autosomal dominant and recessive mutations (ACTG2, MYH11 and LMOD1 gene)[33,34,35].

In our study, this syndrome was suspected only in one affected fetus, while in the remaining cases a LUTO was suspected. Prenatal diagnosis of MMIHS is indeed challenging and successful in less than one third of the cases[36]. However, discriminating MMIHS from LUTO remains crucial because MMIHS, although usually lethal, is rarely associated with significant renal impairment and thus any form of prenatal bladder drainage would be inappropriate[36].

The majority of MMIHS cases in our cohort presented with typical LUTO signs, such as megacystis and bilateral hydronephrosis. This further highlights the importance of considering MMIHS in the differential diagnosis of megacystis with LUTO. To date, this syndrome is typically suspected in female fetuses with coexisting megacystis and normal to increased amniotic fluid. However, in our cohort, fetal gender was not so relevant in predicting MMIHS as three out of five cases were male fetuses. This is in keeping with a systematic review showing that 32% of MMHIS cases occur in boys and polyhydramnios is reported in only 27% of cases[36]. For this purpose, we suggest a new clinical score to discriminate LUTO from cases with non-obstructive megacystis (such as MMIHS), and Tuzovic et al. suggested a set of typical US signs of MMIHS, such as dilated fetal stomach, large atonic bladder with a thin wall and dilated bowel loops in the third trimester[36]. As the gastrointestinal anomalies of MMIHS are scarcely amenable to US diagnosis, fetal MRI can be of help in showing microcolon and dilated esophagus[37]. Although the genetic base of MMHIS is heterogeneous and most cases are sporadic, we would recommend that in the presence of the above-mentioned criteria genetic testing for MMHIS should be carried out, especially before prenatal bladder drainage is considered.

In the subgroup of fetuses with isolated megacystis, our outcome data confirm the report by Bornes et al.: with about half (55%) live born and about 1:6 (15%) diagnosed with vesico-ureteral reflux after birth[9].

However, the most important message of this study is that megacystis can be the common denominator of many more conditions than LUTO only, including complex conditions with poor prognosis such as chromosomal abnormalities or anorectal malformations, as well as merely a sign of isolated urological anomalies with an overall good prognosis.

A limitation of this study is its retrospective nature. In fact, we describe a set of fetal abnormalities and syndromes diagnosed without following a systematic protocol for invasive testing or genetic analyses, but based on local protocols. This implies that other syndromic cases may have been overlooked resulting in an underestimation of the real prevalence of syndromal associations.

To conclude, this study provides an overview of the disorders associated with megacystis and proposes a flowchart (Fig. 2) for the prenatal differential diagnosis of genetic syndromes, chromosomal and developmental abnormalities, focusing on the morphological examination of the fetus. This may be of help in the antenatal work-up and counseling of fetal megacystis.

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Figure Legends

Figure 1. Study population (TOP: 188, IUFD: 50, neonatal death: 68).

Figure 2. Flowchart for the differential diagnosis of fetal megacystis (genetic syndromes, developmental disorders and chromosomal abnormalities).

Figure 3. Outcome of fetuses with isolated megacystis.

Table 1. Severe anomalies and ultrasound markers associated with fetal megacystis.

Abnormal ultrasound findings (n = 293)	**n (%)**
NT ≥ 95 centille	64 (22%)
Single umbilical artery	30 (10%)
Cardiac defects	30 (10%)
Ventricular Septal Defect	3 (1%)
Umbilical cord cyst	27 (9%)
Spine or skeletal anomalies	19 (6%)
Sacrococcygealteratoma	1 (0.3%)
Abdominal wall defects	18 (6%)
Urogenital anomalies	15 (5%)
Intrauterine growth restriction	7 (2%)
Macrosomia	6 (2%)
Macroglossia	1 (0.3%)
Central Nervous System	5 (2%)
Cleft lip/palate	3 (1%)
Fetal Hydrops	8 (3%)
Diaphragmatic hernia	3 (1%)
Plexus choroideus cyst	15 (5%)
Echogenic bowel	11 (4%)
Short long bones	6 (2%)
Ventriculomegaly	2 (0.7%)
Echogenic intracardiac focus	2 (0.7%)
Miscellaneous syndromal markers	16 (5%)

*Miscellaneous syndromal marker included: hypertelorism, strawberry skull, micrognathia, club foot.

Table 2. Final diagnosis and GA at diagnosis of 418 fetal megacystis(TOP: 188, IUFD: 50, neonatal death: 68).

Final diagnosis	**n (%)**	**GA at diagnosis (wks) mean (SD)**
LUTO	222 (53%)	22.6 (±7)
Normal micturition at birth or other isolated urological anomaly	60 (14%)	21.7 (±10)
Miscellaneous congenital syndromes	136 (33%)	18.8 (±7)
- Chromosomalabnormalities	40 (10%)	15.3 (±4)
- Anorectal Malformations	32 (8%)	15.9 (±5)
- Fetal Macrosomia or Overgrowth syndrome	10 (2%)	22.7 (±8)
- MCA and other syndromes	54 (13%)	20 (±7)

TOP, termination of pregnancy; IUFD intrauterine fetal death; MCA, multiple congenital anomalies.

Table 3. Antenatal details and postnatal or postmortem findings in megacystys cases with genetic syndromes, developmental or chromosomal abnormalities.

	Mean GA referral (95%CI) (weeks)	**Mean LBD** (mm)	**Cases with LUTO signs** n (%)	**Oligo- or anhydramnios** n (%)	**Sex** (male%)	**Outcome** (TOP; IUFD or neonatal deaths; alive)	**Associated Anomalies at antenatal US scan**	**Findings at postmortem/postnatal examination**
Chromosomal Abnormalities								
Trisomy 18 or mosaicism (24)	17 (15-20)	25	21 (88%)	7 (29%)	88%	15;9;0	Increased NT; CHD; UCC; omphalocele; skeletal/spine defects	CHD, agenesis of the cerebellar vermis, omphalocele, clubfoot
Trisomy 21 (5)	16 (12-21)	26	3 (60%)	3 (60%)	100%	4;1;0	Increased NT; skeletalanomalies	NA
Turner syndrome or mosaicism (5)	15 (10-21)	15	2 (40%)	1 (20%)	40%	3;1;1	UCC, increased NT	Imperforate anus, facial dysmorphisms, CHD
Trisomy 13 (3)	12 (10-15)	9	3 (100%)	0	100%	3;0;0	CHD, labiopalatoschisis, SUA, polydactyly	NA
Deletion 22q11 syndrome (3)	25	31	3 (100%)	1 (33%)	100%	1;0;2	CHD	Unilateral renal agenesis, CHD, VUR

Total (40)	17 (15-18)	23	32 (80%)	12 (30%)	82%	26;11;3	**Common features: increasedNT**	**Common features: CHD**

Additional chromosomal abnormalities with doubtful clinical significance (n = 5)

	Sex	**GA referral** (weeks)	**LBD** (mm)	**Oligo- or anhydramnios** n (%)	**LUTO signs**	**Outcome**	**Associated anomalies at antenatal US scan**	**Findings at postmortem/postnatal examination**
46,XY, 1.9 Mb duplication, 19q13.33 de novo (1)	M	NA	NA	N	N	Alive	UCC	Delayed motor development; muscular hypotonia; gastroesophageal reflux; ectopic testis;epiphyseal dysplasia, short stature
46,XY, 22q11.2 microduplication + 14q31 duplication (1)	M	37	NA	Y	Y (K; H; O)	Alive	N	PUV + severe VUR (III-IV grade)
46,XX, deletion 5q.35.2 (1)	F	19	NA	Y	Y (ARC; O)	Alive	N	Thethered cord + neurogenic bladder + VUR + multidysplastic kidneys + psychomotorial disabilities
46,X, der (X) t (X; Y) (p22.33;p11.31) (1)	M	21	13	Y	Y (K; H; O)	Alive	N	VUR + bilateral renal displasia and renal insufficiency 46, XX, male
46, XY, t (14;16) (q24.3; q24.1) pat (1)	NA	22	NA	Y	Y (K; ARC; H; O)	TOP	Unilateral renal agenesis (left) + renal dyplasia (right)	Unilateral renal agenesis (left + renal dyplasia (right)

AnorectalMalformations

	Mean GA referral (95%CI) (weeks)	**Mean LBD** (mm)	**Cases with LUTO signs** n (%)	**Oligo- or anhydramnios** n (%)	**Sex** (male%)	**Outcome** (TOP; IUFD or neonatal deaths; alive)	**Associated Anomalies at antenatal US scan**	**Findings at postmortem/postnatal examination**

VACTERL (13)	17 (13-20)	24	10 (83%)	10 (77%)	88%	10;3;0	CHD, unilateral renal agenesis, increased NT, SUA, UCC, FEB	Anal atresia, cloacal anomaly, unilateral renal agenesis, CHD, colon-vesical fistula, limbs anomalies, esophageal atresia, tethered chord, spina bifida, vertebral defect.
CloacalMalformation (6)	17 (13-21)	48	4(67%)	3(50%)	13%	5;1;0	VSD, cystic hygroma, UCC	Cloacalanomaly
OEIS (7)	12 (10-13)	19	2 (29%)	2 (21%)	75%	6;1;0	Omphalocele, SUA, NT	Cloacal anomaly, cloacal exstrophy, limbs anomalies, spina bifida, renal agenesis
CRS (4)	14 (12-16)	25	1(25%)	4 (100%)	50%	3;1;0	Unilateralrenalagenesis, sirenomielia, spina bifida, SUA	Agenesis of sacrum and hypoplasia of the lower extremities
Fraser (2)	21 (20-21)	68	2(100%)	2(100%)	50%	2;0;0	Overgrowth, hypertelorism, club foot, increased NT, renal agenesis	Renal agenesis, syndactyly, imperforate anus, facial dysmorphisms
Total (32)	15 (13-17)	29	23 (82%)	21 (66%)	55%	26;6;0	**Common features: SUA, increased NT, UCC, renal agenesis.**	**Common features: Imperforate anus/anal agenesis, cloacal anomaly, spinal defects, limbs anomalies.**

Overgrowth Syndromes or Fetal Macrosomia (10)								
BWS (2)	22	35	2 (100%)	1 (50%)	100%	1;0;1	Fetal overgrowth; macroglossia, hepatomegaly; skeletal dysplasia	PUV; skeletaldyplasia
Sotos (2)	25 (17-30)	NA	0 (0%)	1 (50%) *1 polyhydramnios	100%	1;0;1	Polyhydramnios	NA
Unknown cause (5)	17 (13-27)	20	2 (40%)	1 (20%) *2 polyhydramnios	100%	2; 0; 3	EFW> 90th centile	VUR, congenitalmegaureter
Cantu (1)	21	15	1 (100%)	0 *1 polyhydramnios	100%	Alive	Polyhydramnios; EFW> 90th centile	VUR, facial dysmorphisms, pulmonary artery stenosis
Total (10)	22 (15-29)	27	5 (50%)	6 (60%)	100%	4;0;6	**Common features: fetal overgrowth and polyhydramnios**	**Common features: VUR or PUV**
MMIHS (5)	16 (13-21)	42	5 (100%)	1 (20%)	60%	0;5;0	Increased NT, club foot	NA
Smith-Lemli-Opitz (2)	16 (11-27)	NA	2 (100%)	2 (100%)	100%	1;0;1	Shortened long bones; increased NT	Urethral atresia, hypospadia, ureteropelvis stenosis, Polydactyly, CHD, cleft palate, micrognathism
Othermiscellaneoussyndromes (n = 4)								
	Sex	**GA at referral** (weeks)	**LBD** (mm)	**Oligo- or anhydramnios** n (%)	**LUTO signs**	**Outcome**	**Associated anomalies at antenatal US scan**	**Findings at postmortem/postnatal examination**

Morrissyndrome (1)	M	35	57	0	N	Alive	N	
Ochoasyndrome (1)	M	33	54	0	N	Alive	N	
SpinalMuscularAtrophy (1)	M	16	35	0	Y (K; ARC)	Alive	NT; UCC; Absent DV; Hydrops	Arthrogryposis + neurogenicbladder
Marcus Gunn Jaw Winking syndrome (1)	M	21	NA	0	N	Alive	N	PUV + VUR + Duplex Collecting system

GA, gestational age; BLD, bladder longitudinal diameter; AF amount, amniotic fluid throughout pregnancy; Oligo, oligohydramnios; Ani, anhydramnios; Poli, polihydramnios; CRS, caudal regression syndrome; BWS, Beckwith-Wiedemann syndrome; MMIHS, megacystis-microcolon-intestinal hypoperistalsis; UCC, umbilical cord cyst; NT, nuchal translucency ; CHD, congenital heart defect; SUA, single umbilical artery; FEB, fetal echogenic bowel; VSD, ventricular septal defect; N, no; NA, not available; M, male; F, female; VUR, vesico-ureteral reflux; EFW, estimated fetal weight; ARC, Abnormal renal cortical appearance; O, oligohydramios ; K, keyhole sign ; H, hydronephrosis; A, anhydramnios; PUV, posterior urethral valves; VUR, vesico-ureteral reflux; EFW, estimated fetal weight.

Table 4. Outcome and postnatal renal function of cases with isolated LUTO.

Outcome (n = 222)	
Termination of pregnancy	54 (24.3%)
Perinatal death	39 (17.6%)
Alive	129 (58.1%)
Cause of obstruction (n = 181)	
Posterior urethral valves (PUV)	83 (46%)
Urethral atresia	5 (3%)
Urethral stenosis and others	93 (51%)
Postnatal renal function (n = 80)	
eGFR (mL/min/1.73m^2)	63 (3 - 162)
Severly impaired renal function (eGFR< 30 mL/min/1.73m^2)	16 (20%)

Categorical variable are expressed as number and percentage (n, %) Numerical variable are expressed as mean (95%CI) or median. (range)

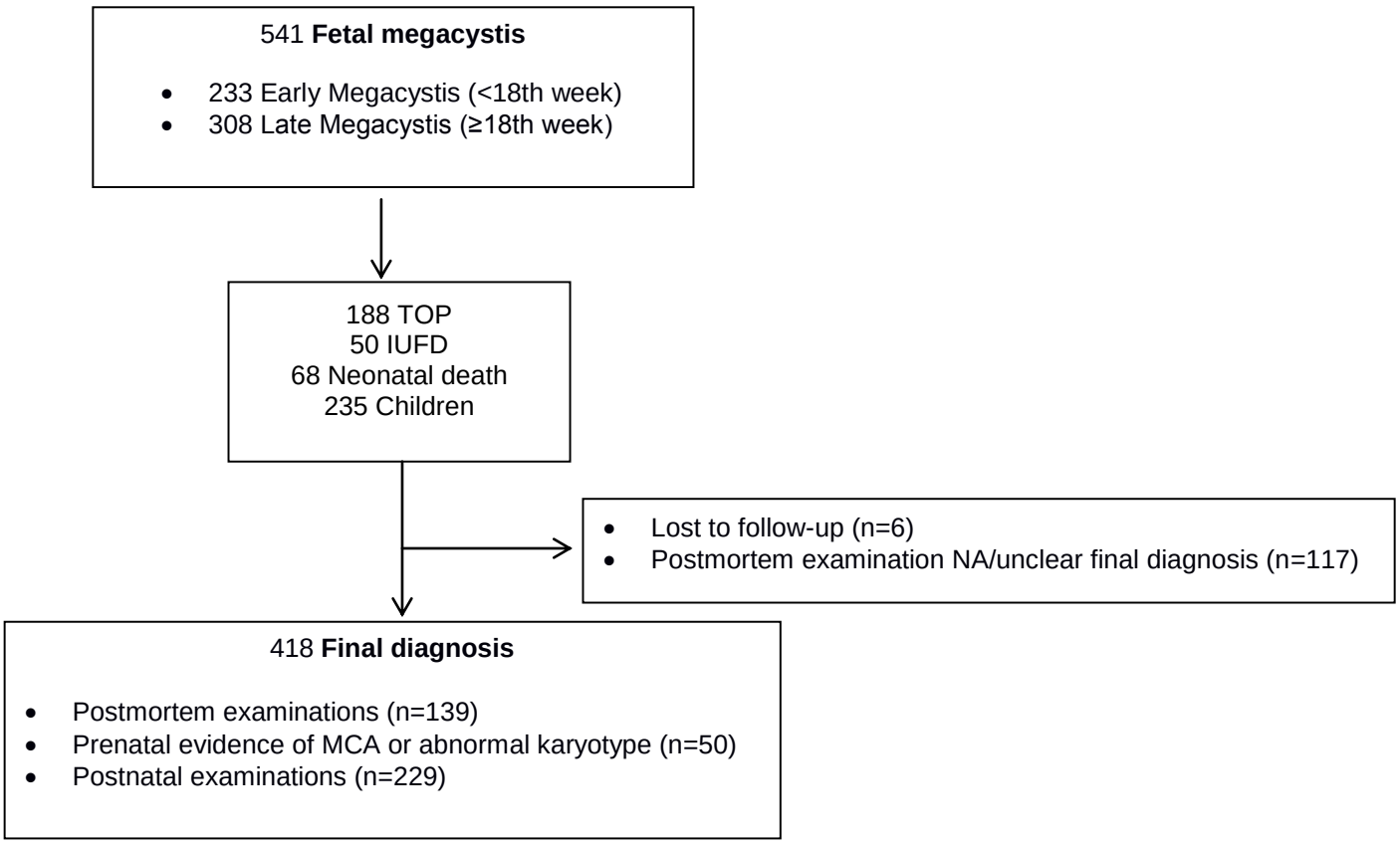

Figure 2.

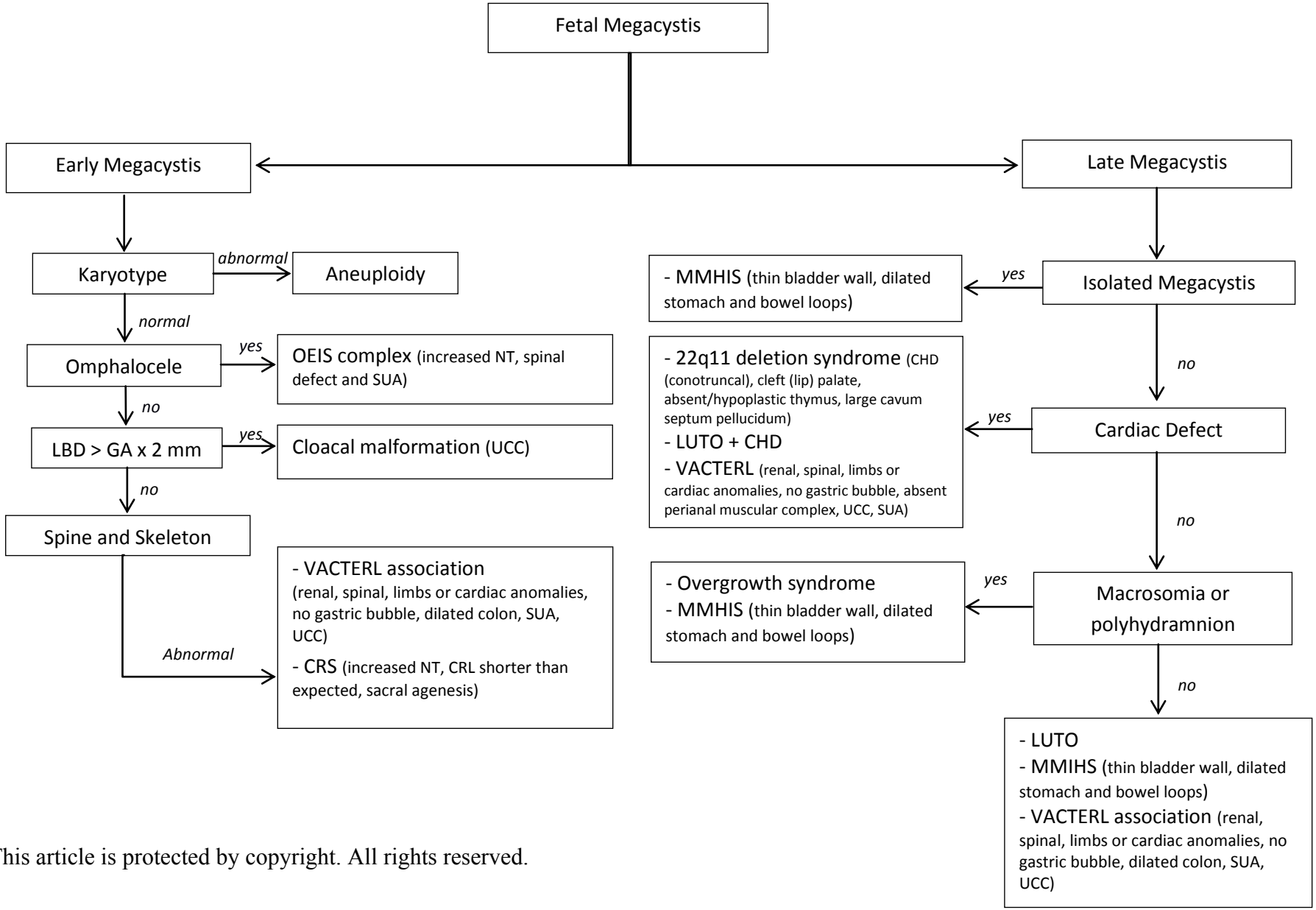

Figure 3.